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Our Ref.: 427.010-1-DIV-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: : B. Kifle
DENNIS BIGG et al :
Serial No.: 09/612,382 : Group: 1624
Filed: July 7, 2000 :
For: NEW...CONTAINING THEM :.

475 Park Avenue South
New York, N.Y. 10016
January 7, 2004

BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

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Patents, P.O. Box 1450, Alexandria, VA 22313-1450

REAL PARTY IN INTEREST

The real party in interest is the Societe De Conseils De Recherches
D'Applications Scientifiques (S.C.R.A.S.) by means of an assignment recorded in the
Patent Office.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Appellant, the Appellant's
legal representative or assignee which will directly affect or be directly affected by or
have a bearing on the Board's decision in the pending appeal.

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STATUS OF THE CLAIMS

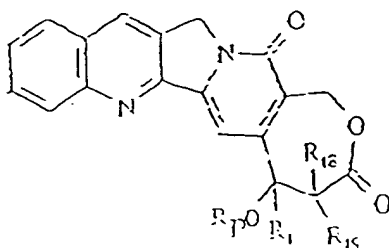
The claims in the application are 5 to 8 and 18 to 24. Claims 5 to 8, 18 and 24 have been objected to but are deemed drawn to allowable subject matter.

STATUS OF THE AMENDMENTS

No amendment after final rejection has been submitted.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating cancer by the administration of a substituted camptothecin with a 7-ring member β -hydroxy lactone ring of the formula



or a non-toxic, pharmaceutically acceptable salt thereof to a patient in need of such treatment.

THE ISSUES

Claims 18 to 23 stand rejected under 35 USC 112, second paragraph, as being indefinite since the Examiner was of the opinion that the phrase “pharmaceutically acceptable substituted camptothecin” is deemed to render the claims indefinite since one skilled in the art could not determine what the intended substituents are and where the substituents are supposed to be. The Examiner is of the opinion that without the recitation of the substituents in the claims, the claims do not adequately define the invention.

Claims 18 to 23 were rejected under 35 USC 112, first paragraph, as containing subject matter which is not described in the specification so as to enable one skilled in the art, to which it pertains, to make and/or use the invention. The Examiner deems the specification is not adequately enabling for the scope of the compounds embraced by the claims. The Examiner states there is no reason why a claim drawn in Applicants’ method should be limited to those compounds which are shown to be new and useful and an Applicant is not entitled to a claim for the use of a large group of compounds merely on the basis of a showing that a selected few are useful and there is a general suggestion of a similar utility of others. The Examiner is of the opinion that there is no enabling disclosure for compounds that are substituted at the pyrrolidine or substituents adjacent to the oxygen on the lactone ring.

GROUPING OF THE CLAIMS

The claims are not properly grouped together since the Examiner has indicated that claims 5 to 8 and 24 are drawn to allowable subject matter and presumably, the generic claims are deemed to be allowable with the exception of the breadth and enabling disclosure rejections.

APPLICANTS' ARGUMENTS

Applicants respectfully request the Board of Patent Appeals and Interferences to reverse the Examiner's rejections since it is deemed that the specification clearly supports the present terminology of the generic claims and the term "pharmaceutically accepted substituted camptothecin" is not too broad and indefinite.

The Board's attention is directed to the paragraph bridging pages 1 and 2 of the specification wherein it is stated that "the new analogs of camptothecin differ from all the other known derivatives in that they contain a β -hydroxy lactone or its open hydroxy carboxylic form instead of an α -hydroxy lactone or α -hydroxy carboxylic form and the salts thereof". Furthermore, in the first few lines, it also defines the derivatives of the camptothecin as being "a compound having the same structural skeleton as that of camptothecin...with or without other chemical substitutions on the skeletal structure. Different derivatives of camptothecin are well known by specialists as described hereafter."

It goes on in the first full paragraph on page 2 to state “An analog of camptothecin according to the invention can therefor contain substitutions on the indolizino [1,2-b] quinoline fragment” and then goes on to give examples thereof. Therefore, clearly the present terminology which is directed to unsubstituted or pharmaceutically acceptable substituted camptothecin with a 7-ring member β -hydroxy ring of the formula in claim 1 is described in the specification as filed and the claims are not broader than the broadest definition in the disclosure.

The Board of Patent Appeals and Interference’s attention is directed to the declaration filed August 2, 2002 which summarizes the results of tests done by the assignee of the present application which tested 137 compounds falling within the scope of the application and all were useful for treating various cancers. The cancers included cancer of the bladder, the breast, the central nervous system, the colon, leukemia, lung and prostate and all of the compounds were active against the various cancers, obviously, varying in degree depending upon the specific compound. However, unequivocally, each and every compound tested was active and this is completely surprising. It is deemed that Applicants have clearly demonstrated that the main portion of the structure is the 7-ring member β -hydroxy lactone ring and unequivocally that all of the claimed compounds are unexpectedly suitable for the treatment of the various cancers and the claims are of sufficient scope and are clearly within the scope of the disclosure. It should be noted that the test employed by Applicants is an art recognized test as can be seen from the papers submitted with the declaration.

Applicants' invention resides in the fact that they are drawn to a substituted or unsubstituted camptothecin with a 7-ring member β -hydroxy lactone ring and this can be clearly seen from the structural formula in claim 18 at the present time. As pointed out on pages 1 and 2 of the application as filed, the novel compounds differ from all known derivatives of camptothecin in that they contain the β -hydroxy lactone instead of an α -hydroxy lactone and its pharmaceutical salts. Apart from this, the compounds can have the same structural skeleton as that of the known camptothecins with or without other chemical substitutions on the skeletal structure which are well known to those skilled in the art Applicants have already tested 137 compounds as can be seen from the Thurieau declaration and all have activity.

As pointed out to the Examiner at an interview, the novelty resides in the fact that the 7-membered ring β -lactones are active for treating cancers which was completely surprising for those skilled in the art. In the preliminary amendment dated July 7, 2000 filed with the application, there were three publications submitted and the Examiner's attention is directed to the same and this would lead one skilled in the art away from using a 7-ring member β -hydroxy lactone for the treatment of cancer. The Examiner's attention is directed thereto. Even after publication of Applicants' initial disclosure with respect to the novel compounds, there were publications indicating that those skilled in the art were completely surprised that the 7-ring member β -hydroxy lactone ring compounds were active. Applicants have submitted a declaration by Christophe Thurieau

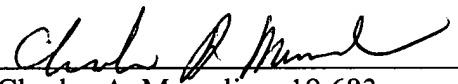
which reports on the testing of 137 compounds falling within the scope of the above application and all of them were useful for the treating of various cancers. The cancers included cancer of the bladder, the breast, the central nervous system, the colon, leukemia, lung and prostate and all of the compounds were active against the various cancers, obviously, varying in degree depending upon the specific compound. However, they were all active and this is completely surprising. It is deemed that Applicants have clearly demonstrated that the claimed compounds are unexpectedly suitable for the treatment of the various cancers and that the claims are of sufficient scope and are clearly supported by the specification as filed.

With respect to the rejection based upon a non-enabling disclosure, it is deemed that the specification is enabling for the present claims. The specification clearly teaches one skilled in the art how to produce the various compounds and Applicants have not merely selected a few compounds which are useful because there have been 137 compounds submitted to the Patent Office, all of which have the property. Moreover, the compounds differ from the known compounds, as pointed out in the specification, only on the basis of a 7-ring lactone rather than a 6-ring lactone and it is well understood by one skilled in the art that all of the compounds falling within the scope of Applicants' claims would have the same utility. Therefore, it is deemed that the specification is enabling for the claims of the present scope.

CONCLUSION

Applicants request that the Board of Patent Appeals and Interferences reverse the Examiner's rejections since Applicants have clearly pointed out where the claims are supported in the specification and have clearly demonstrated by tests on 137 compounds that the scope of the claims is clearly supported by the record and is enabling. Applicants have complied with all the necessary requisites the granting of Letters Patent and it is requested that the Board reverse the Examiner's rejections. Three copies of the brief on appeal are being filed as well as PTO Form-2038 authorizing the \$330.00 appeal brief filing fee.

Respectfully submitted,
Muserlian, Lucas and Mercanti



Charles A. Muserlian, 19,683
Attorney for Applicants
Tel. # (212) 661-8000

CAM:ds
Enclosures

Our Ref.: 427.010-1-DIV-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	B. Kifle	:
DENNIS BIGG et al	:		:
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For: NEW...CONTAINING THEM	:		:

600 Third Avenue
New York, N.Y. 10016

APPENDIX

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The claims on appeal are:

5. A compound according to claim 3, characterized in that is one of the following compounds :

- 5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]-quinoline-3,15-dione ;

- 5,12-diethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;

- 8-ethyl-8-hydroxy-2,3,8,9,12,15-hexahydro-10*H*,13*H*-[1,4]dioxino[2,3-*g*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13-dione;

- 10-(benzyloxy)-5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;

- 11-[(dimethylamino)methyl]-5-ethyl-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-9-fluoro-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 7-ethyl-7-hydroxy-7,8,11,14-tetrahydro-9*H*,12*H*-[1,3]dioxolo[4,5-*g*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-9,12-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 9,11-dichloro-5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 10-chloro-5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5,10-dihydroxy-11-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 5,12-diethyl-9-fluoro-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-12-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methoxy-12-[(4-methyl-1-piperazinyl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methoxy-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-12-[(4-methyl-1-piperazinyl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione ;
- 5-ethyl-5-hydroxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-10-fluoro-5-hydroxy-12-[(4-methyl-1-piperazinyl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-10-fluoro-5-hydroxy-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-[(4-methyl-1-piperazinyl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 8-ethyl-8-hydroxy-16-[(4-methyl-1-piperazinyl)methyl]-2,3,8,9,12,15-hexahydro-10*H*,13*H*-[1,4]dioxino[2,3-*g*] oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13-dione;

- 9-chloro-5-ethyl-10-fluoro-5-hydroxy-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[3,6-dihydro-1(2*H*)-pyridinylmethyl]-5-ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-[(4-methyl-1-piperidinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-(1-pyrrolidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-[(4-methyl-1-piperazinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(dimethylamino)methyl]-5-ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-[(4-methyl-1-piperazinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[[benzyl(methyl)amino]methyl]-9-chloro-5-ethyl-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(4-benzyl-1-piperazinyl)methyl]9-chloro-5-ethyl-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 12-[(4-benzyl-1-piperazinyl)methyl]5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(4-benzyl-1-piperazinyl)methyl]5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(dimethylamino)methyl]-5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(diethylamino)methyl]-5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-[(4-methyl-1-piperidinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-(1-pyrrolidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[3,6-dihydro-1(2*H*)-pyridinylmethyl]5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione ;
- 12-[(diisobutylamino)methyl]-5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methoxy-12-[(4-methyl-1-piperazinyl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methoxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-12-[(dimethylamino)methyl]-5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 9-chloro-5-ethyl-5-hydroxy-10-methoxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[3,6-dihydro-1(2*H*)-pyridinylmethyl]-5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-10-methoxy-12-[(4-methyl-1-piperidinyl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
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- 10-(benzyloxy)-5-ethyl-9-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-3,15-dioxo-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinolin-5-yl 2-aminoacetate;
- 5-ethyl-9,10-difluoro-3,15-dioxo-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinolin-5-yl 3-aminopropanoate;
- 2,9-diethyl-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione;

- 9-ethyl-9-hydroxy-2-methyl-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione;
- 2-benzyl-9-ethyl-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione;
- 2-benzyl-9-ethyl-5-fluoro-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]-oxazino[5,6-*f*]oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione;
- (+)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- (+)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinolin-12-ylmethyl]4-methylhexahydropyridine;

or a pharmaceutically acceptable salt of the latter.

6. A compound according to claim 5, characterized in that is one of the following compounds :

- 5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5,12-diethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 8-ethyl-8-hydroxy-2,3,8,9,12,15-hexahydro-10*H*,13*H*-[1,4]dioxino[2,3-*g*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13-dione;
- 5-ethyl-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 9-chloro-5-ethyl-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 7-ethyl-7-hydroxy-7,8,11,14-tetrahydro-9*H*,12*H*-[1,3]dioxolo[4,5-*g*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-9,12-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 9,11-dichloro-5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 10-chloro-5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5,12-diethyl-9-fluoro-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-12-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-[(4-methyl-1-piperazinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[3,6-dihydro-1(2*H*)-pyridinylmethyl]5-ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-[(4-methyl-1-piperidinyl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-(1-pyrrolidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-[(4-methyl-1-piperazinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(dimethylamino)methyl]5-ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-[(4-methyl-1-piperazinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(4-benzyl-1-piperazinyl)methyl]9-chloro-5-ethyl-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(diethylamino)methyl]-5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-[(4-methyl-1-piperidinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-(1-pyrrolidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 12-[3,6-dihydro-1(2*H*)-pyridinylmethyl]5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione ;
- 12-[(diisobutylamino)methyl]5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methoxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-12-[(dimethylamino)methyl]5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methoxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-10-methoxy-12-[(4-methyl-1-piperidinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-[(4-methyl-1-piperidinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione ;
- 2,9-diethyl-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- 9-ethyl-9-hydroxy-2-methyl-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- 2-benzyl-9-ethyl-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- 2-benzyl-9-ethyl-5-fluoro-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- (+)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (+)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinolin-12-ylmethyl]4-methylhexahydropyridine;

or a pharmaceutically acceptable salt of the latter.

7. A compound according to claim 6, characterized in that is one of the following compounds :

- 5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]-quinoline-3,15-dione;

- 5,12-diethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;

- 8-ethyl-8-hydroxy-2,3,8,9,12,15-hexahydro-10*H*,13*H*-[1,4]dioxino[2,3-*g*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13-dione;

- 5-ethyl-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-9-fluoro-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 9-chloro-5-ethyl-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;

- 7-ethyl-7-hydroxy-7,8,11,14-tetrahydro-9*H*,12*H*-[1,3]dioxolo[4,5-*g*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-9,12-dione;

- 9-chloro-5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 10-chloro-5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5,12-diethyl-9-fluoro-5-hydroxy-10-methoxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-12-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5-hydroxy-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-[(4-methyl-1-piperidiny)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9,10-difluoro-5-hydroxy-12-(1-pyrrolidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-(4-morpholinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 9-chloro-5-ethyl-5-hydroxy-10-methyl-12-[(4-methyl-1-piperazinyl)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[(diethylamino)methyl]5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5-hydroxy-10-methyl-12-[(4-methyl-1-piperidiny)methyl]1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 12-[3,6-dihydro-1(2*H*)-pyridinylmethyl]5-ethyl-9-fluoro-5-hydroxy-10-methyl-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione ;
- 5-ethyl-9-fluoro-5-hydroxy-10-methoxy-12-(1-piperidinylmethyl)-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- 5-ethyl-9-fluoro-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione ;
- 2,9-diethyl-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- 9-ethyl-9-hydroxy-2-methyl-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- 2-benzyl-9-ethyl-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]oxazino[5,6-*f*]-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- 2-benzyl-9-ethyl-5-fluoro-9-hydroxy-1,2,3,9,10,16-hexahydro-13*H*-[1,3]-oxazino[5,6-*f*]oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-11,14-dione ;
- (+)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- (+)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinolin-12-ylmethyl]4-methylhexahydropyridine;

or a pharmaceutically acceptable salt of the latter.

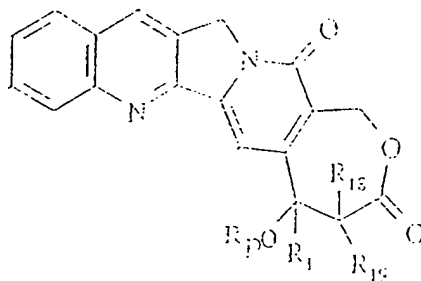
8. A compound according to claim 7, characterized in that is one of the following compounds :

- 5-ethyl-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-10-fluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione;
- 5-ethyl-9-fluoro-5,10-dihydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,15-dione ;
- (+)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (+)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinolin-12-ylmethyl]4-methylhexahydropyridine;

or a pharmaceutically acceptable salt of the latter.

18. The method of treating a cancer selected from the group consisting of leukemia, colon cancer, lung cancer, prostate and breast cancer in warm-blooded animals comprising administering to warm-blooded animals in need thereof a unsubstituted or pharmaceutically acceptable substituted camptothecin with a 7-ring member β -hydroxy lactone ring of the formula



wherein R_1 is selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkenyl and alkynyl of 2 to 6 carbon atoms haloalkyl of 1 to 6 carbon atoms, alkoxy alkyl of 2 to 12 carbon atoms and alkylthioalkyl of 2 to 12 carbon atoms. R_p is hydrogen or an easily cleavable group, R_{18} and R_{19} are individually selected from the group consisting of hydrogen, halogen, OH and alkyl and alkoxy of 1 to 6 carbon atoms and its non-toxic, pharmaceutically acceptable salts.

19. The method of claim 18 wherein R_1 is ethyl.
20. The method of claim 18 wherein R_{18} and R_{19} are hydrogen.
21. The method of claim 19 wherein R_{18} and R_{19} are hydrogen.
22. The method of claim 18 wherein R_p is hydrogen.
23. The method of claim 19 wherein R_p is hydrogen.
24. The method of claim 18 wherein the camptothecin is (+)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione or (+)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinolin-12-yl methyl]-4-methyl-hexahydropyridium chloride.